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FDA Approves Symbyax® as First Medication for Treatment-Resistant Depression

New Indication is One of Three FDA Approvals Spanning Lilly Neuroscience Brands

INDIANAPOLIS – March XX, 2009 – The U.S. Food and Drug Administration (FDA) has approved a new indication for Symbyax® (olanzapine and fluoxetine HCl capsules), Eli Lilly and Company (NYSE: LLY) announced today. Symbyax is now the first drug approved by the FDA for the acute treatment of treatment-resistant depression (TRD).

"Living with major depressive disorder is difficult and distressing for anyone, but even more so for patients whose symptoms continue despite treatment," said Lilly Medical Director Dr. Sara Corya. "Until today, there has been no approved medication for treatment-resistant depression. Now, after two failed attempts with other antidepressants, doctors and patients have a new treatment option."

In other actions, the FDA approved two new combination indications for Zyprexa® (olanzapine) and fluoxetine for the acute treatment of bipolar depression and TRD. Lilly originally developed Prozac® (fluoxetine HCl), the branded version of fluoxetine.

Additionally, the format of the product labels was updated according to the Physician's Labeling Rule (PLR), which many consider easier to understand. Additions were also made to the Medication Guides for Symbyax and Prozac, and a new Medication Guide was created for Zyprexa. Medication Guides include information for patients about potential risks associated with a particular product.

"Lilly maintains its commitment to patients by the continued research of Zyprexa, Symbyax, and Prozac," said Dr. Cherri Miner, Lilly neuroscience senior medical director. "Today's new indications confirm that these medications are valuable tools for patients in the fight against severe and disabling mental illness, and expand treatment options for prescribers and patients."

Indication Details:

1. The new Symbyax TRD indication is for acute treatment of adult patients with major depressive disorder who have not responded to two separate trials of different antidepressants of adequate dose and duration in their current episode.
2. Zyprexa, in combination with fluoxetine, is now approved for the acute treatment of TRD in adults.
3. Symbyax was the first drug approved by the FDA for acute treatment of bipolar depression in adults in 2003. Zyprexa, in combination with fluoxetine, is now approved for the same indication.

With these FDA approvals, clinicians in the United States have the choice to use the single pill option (Symbyax), or the two drugs (Zyprexa and fluoxetine) together, allowing physicians to tailor treatment to each patient's needs. Neither Zyprexa nor fluoxetine are indicated as monotherapy for bipolar depression or TRD.

Additional Label Changes

In addition to the new indications, Lilly has updated the Symbyax and Zyprexa labels to include additional information regarding weight gain, hyperglycemia, and hyperlipidemia following the FDA's review of clinical trial data that Lilly submitted to the FDA between August 2007 and July 2008. In the course of this review, Lilly provided data from several large databases, including analyses of placebo-controlled data, comparator-controlled data, long-term data and special populations, including antipsychotic-naïve patients.

Symbyax and Zyprexa in Combination with Fluoxetine Supportive Study Details for TRD

The data package submitted to the FDA supporting the approval of Symbyax for TRD as well as the approval of Zyprexa in combination with fluoxetine for TRD, included one pivotal trial and data from three supportive trials and one inconclusive trial. The TRD-related label language includes efficacy data from three of these clinical studies (n=579). Acute safety information was based on a total of 10 studies. Doses evaluated in these studies ranged from 6-18 mg for olanzapine and 25-50 mg for fluoxetine in fixed combination.

- An eight-week randomized, double-blind, controlled study was conducted to evaluate the efficacy of Symbyax in patients (n=300) who met the fourth edition of "Diagnostic and Statistical Manual of Mental Disorders" (DSM-IV) criteria for major depressive disorder (MDD) and did not respond to two antidepressants of adequate dose and duration in their current episode. Patients who were not responding to an antidepressant in their current episode entered an eight-week open-label fluoxetine lead-in, and then non-responders were randomized (1:1:1) to receive an eight-week trial of Symbyax, olanzapine, or fluoxetine. Symbyax was flexibly dosed between 6/50 mg, 12/50 mg, and 18/50 mg (olanzapine/fluoxetine dose). Results from this study yielded a greater statistically significant reduction in mean total Montgomery Åsberg Depression Rating Scale (MADRS) scores from baseline to endpoint for Symbyax versus fluoxetine and olanzapine alone.
- A second study of 28 patients who met the same criteria for TRD demonstrated statistically significant greater reductions in MADRS scores for Symbyax versus fluoxetine and olanzapine alone.
- A third study demonstrated statistically significant greater reductions in total MADRS scores for Symbyax versus fluoxetine or olanzapine alone, when analyzed in a subpopulation of depressed patients (n=251) who met the same criteria for treatment resistance.
- Although not cited in the approved label, two additional studies were included in the sNDA data package. One of the trials provided statistically significant supporting data for Symbyax in the acute treatment of TRD, while the other trial was inconclusive.

- An integrated analysis of all five studies provided to the FDA yielded a statistically significant greater reduction in mean total MADRS scores from baseline to endpoint in the defined population for patients treated with Symbyax (-12.2) vs. fluoxetine (-8.5, p=0.015) and olanzapine (-7.7, p=0.007) and greater statistically significant remission rates (p=<0.05) for patients treated with Symbyax (25.5 percent), vs. fluoxetine (17.3 percent) and olanzapine (14.0 percent).

Adverse events that were reported in five percent or more of Symbyax-treated patients in these trials and at twice the rate of placebo were weight gain, increased appetite, dry mouth, somnolence and fatigue. This is consistent with the current safety information provided in the Symbyax label.

Pivotal Studies for Bipolar Depression

Approval was based on the results of two identical, eight-week, randomized, double-blind, controlled studies of patients diagnosed with bipolar depression. Zyprexa and fluoxetine in combination (6/25, 6/50, or 12/50 mg/day respectively) were compared to both Zyprexa alone (5 to 20 mg/day) and placebo. The primary outcome was symptom improvement based on the Montgomery-Åsberg Depression Rating Scale (MADRS). Both trials showed that combination therapy with Zyprexa and fluoxetine resulted in a statistically significant greater improvement compared to Zyprexa alone and placebo.

- In one eight-week controlled trial, combination therapy with Zyprexa and fluoxetine (n=42) was superior to both Zyprexa monotherapy (n=169) and placebo (n=174) in the reduction of the MADRS total score.
- In a second eight-week controlled trial, combination therapy with Zyprexa and fluoxetine (n=40) was superior to both Zyprexa monotherapy (n=182) and placebo (n=181) in the reduction of MADRS total score.

About Treatment-Resistant Depression

It is estimated that up to 35 percent of patients with depression – or approximately two percent of the general population – fail to achieve an adequate response to two respective antidepressant drug therapy attempts.[1] The exact causes of depression and why some people do not respond to initial pharmacological therapy is not known.[2]

About Bipolar Depression

Depressive episodes associated with bipolar I disorder (also known as bipolar depression) refers to the depressive phase of bipolar disorder, a complex mental illness characterized by debilitating swings in mood. The swings range from manic episodes, marked by abnormal euphoria, elation and irritability, to episodes of deep depression, marked by extreme sadness and difficulty functioning.[3]

Safety Information for Symbyax and Concomitant Use of Zyprexa and Fluoxetine

Symbyax is indicated in the United States for the acute treatment of bipolar depression and treatment-resistant depression in adults. Treatment-resistant depression is defined as major depressive disorder in adults who do not respond to two separate trials of different antidepressants of adequate dose and duration in the current episode.

Antidepressants can increase suicidal thoughts and behaviors in children, teens and young adults. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for worsening depression symptoms, unusual changes in behavior or thoughts of suicide. Patients and caregivers should be especially observant within the first few months of treatment or after a change in dose. Symbyax is not approved for children and adolescents.

Symbyax is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

In addition, compared to elderly patients with dementia-related psychosis taking a placebo, there was a significantly higher incidence of cerebrovascular adverse events in elderly patients with dementia-related psychosis treated with olanzapine, a component of Symbyax.

Symbyax should not be used with a monoamine oxidase inhibitor (MAOI) or within at least 14 days of discontinuing an MAOI. At least five weeks should be allowed after stopping Symbyax before starting an MAOI. Thioridazine should not be given with Symbyax or within at least five weeks after stopping Symbyax. Concomitant use of Symbyax in patients taking pimozide is contraindicated. Symbyax is contraindicated in patients with known hypersensitivity to the product or any component of the product.

As with all antipsychotic medications, a potentially fatal condition known as Neuroleptic Malignant Syndrome (NMS) has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. Physicians should consider the risks and benefits when prescribing Symbyax to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level. Patients taking Symbyax should be monitored regularly for worsening of glucose control. Patients starting treatment with Symbyax should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia,

polyuria, palyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Undesirable alterations in lipids have been observed with Symbyax use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using Symbyax, is advised. Clinically significant, and sometimes very high, elevations in triglyceride levels have been observed with Symbyax use. Clinically meaningful increases in total cholesterol have also been seen with Symbyax use.

Potential consequences of weight gain should be considered prior to starting Symbyax. Patients receiving Symbyax should receive regular monitoring of weight.

Development of a potentially life-threatening serotonin syndrome or NMS-like reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) alone, including Symbyax treatment, but particularly with concomitant use of serotonergic drugs, including triptans, with drugs which impair serotonin metabolism, including MAOIs, or with antipsychotics or other dopamine antagonists. If these events occur, treatment with Symbyax and any concomitant serotonergic or antidopaminergic agents should be discontinued immediately and supportive symptomatic treatment should be initiated.

If rash or other possibly allergic phenomena appear for which an alternative etiology cannot be determined, immediate discontinuation is recommended.

Patients being treated with Symbyax should be screened for bipolar disorder and monitored for mania/hypomania.

As with all antipsychotic treatment, prescribing should be consistent with the need to minimize Tardive Dyskinesia (TD). The risk of developing TD and the likelihood that it will become

irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Symbyax may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period. Particular caution should be used in patients with known cardiovascular disease, cerebrovascular diseases, or those predisposed to hypotension.

Symbyax should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Symbyax with non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, warfarin or other drugs that affect coagulation.

As with other antidepressants, Symbyax has been associated with cases of clinically significant hyponatremia that appeared to be reversible when Symbyax was discontinued.

As with any CNS-active drug, Symbyax has the potential to impair judgment, thinking or motor skills.

As with other drugs that antagonize dopamine receptors, Symbyax elevates prolactin levels, and a modest elevation persists during administration.

Because of the long elimination half-lives of fluoxetine and its major metabolite, changes in dose will not be fully reflected in plasma for several weeks.

Other potentially serious adverse events include body temperature elevation, trouble swallowing and adverse events upon discontinuation of treatment.

The most common (≥5% and at least twice that for placebo) treatment-emergent adverse event associated with Symbyax in placebo-controlled clinical trials were weight gain, increased appetite, dry mouth, somnolence, fatigue, peripheral edema, tremor, sedation, hypersonmia, disturbance in attention, and blurred vision.

Full prescribing information, including boxed warnings, is available at www.symbyax.com, www.zyprexa.com and www.prozac.com.

About Lilly

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers -- through medicines and information -- for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

This press release contains forward-looking statements about Zyprexa, Prozac, and Symbyax. These statements reflect management's current beliefs; however, as with any pharmaceutical product there are risks and uncertainties in the process of research and development, regulatory review, and commercialization. In addition, there are no guarantees that the products will continue to be commercially successful or will be successful in these new indications. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

Symbyax® (olanzapine and fluoxetine HCl capsules, Lilly)

Zyprexa® (olanzapine, Lilly)

Prozac® (fluoxetine HCl capsules, Lilly)

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[1] Nemeroff, C. Prevalence and Management of Treatment-Resistant Depression. J. Clin Psychiatry 2007; 68 (suppl. 8): 17-25.
[2] National Institutes of Health. Medline Plus. Major Depression. Accessed February 24, 2009. Available at http://www.nlm.nih.gov/medlineplus/ency/article/000945.htm.
[3] Bipolar Disorder. Published by National Institute of Mental Health. NIH Publication No. 02-3679; Printed 2001, Reprinted September 2002. [Online] http://www.nimh.nih.gov/publicat/bipolar.cfm. 4 March 2009 date last accessed.